When and how to initiate SGLT2i in CKD

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4 Things to know about CKD and SGLT2i

When and how to initiate SGLT2 inhibitor therapy in Chronic Kidney Disease (CKD)

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UCL DEPARTMENT OF RENAL MEDICINE

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Disclosures: Honoraria and/or consultancy fees from Amgen, AstraZeneca (ongoing), Boehringer Ingelheim, Bayer, GlaxoSmithKline, Gilead, Janssen, Merck Sharp and Dohme, Mundipharma, Takeda, Vifor and Zydus.

Inclusion Criteria: SGLT2 inhibitor trials in Chronic Kidney Disease

	CREDENCE[1]	DAPA-CKD[2]	EMPA-KIDNEY[3]
Published	April 2019	September 2020	November 2022
SGLT2 inhibitor	Canagliflozin	Dapagliflozin	Empagliflozin
Non diabetic patients	No	Yes	Yes
eGFR range	30 to 90 ml/min/1.73m^2	25 to 75 ml/min/1.73m^2	20 to 90 ml/min/1.73m^2
UACR range	300-5000 mg/g 33.9-565 mg/mmol	200-5000 mg/g 22.6-565 mg/mmol	> 200 mg/g (22.6 mg/mmol) if eGFR >45 ml/min/1.73m^2

[1]Perkovic V et al, NEJM 2019;380:2295-2306
[2]Heerspink HJL et al, NEJM 2020;383:1436-1446
[3]Herrington W et al, NEJM Moa2204233

Case 1: White male with Type 2 diabetes and CKD

- 68 year old white man with type II diabetes for 10 years
- Weight 135 kg, BMI 31.8 kg/m^2
- Early diabetic retinopathy
- Metformin 500 mg bd, Gliclazide 40 mg bd
- Ramipril 10 mg od, Atorvastatin 20 mg od
- Annual review
- BP 155/95 mmHg

eGFR 52 ml/min/1.73m^2 (previously 58)
UACR 672 mg/mmol (previously 309)
(UACR 5947 mg/g previously 2735)
HbA1c 72 mmol/mol (8.7%)

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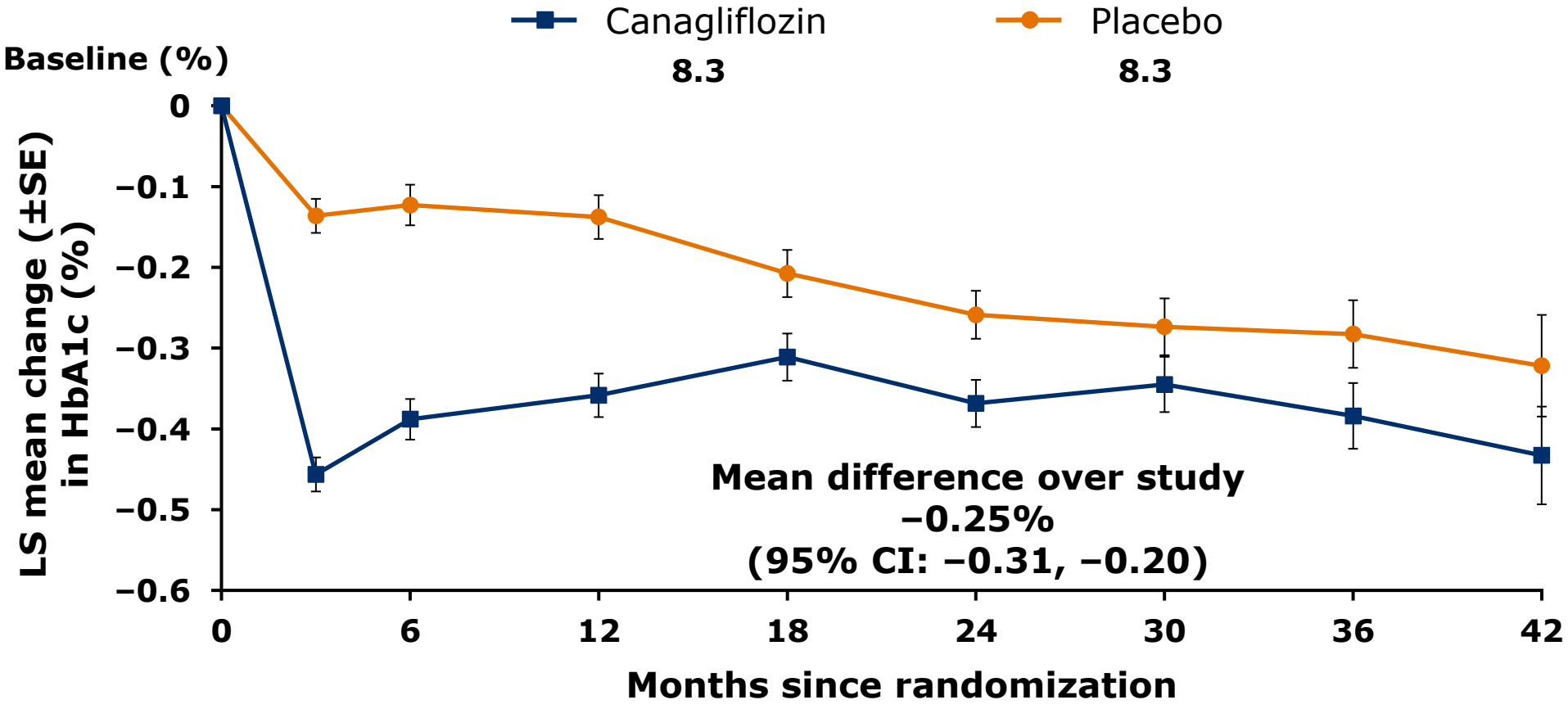
CREDENCE trial: Effects on HbA1c

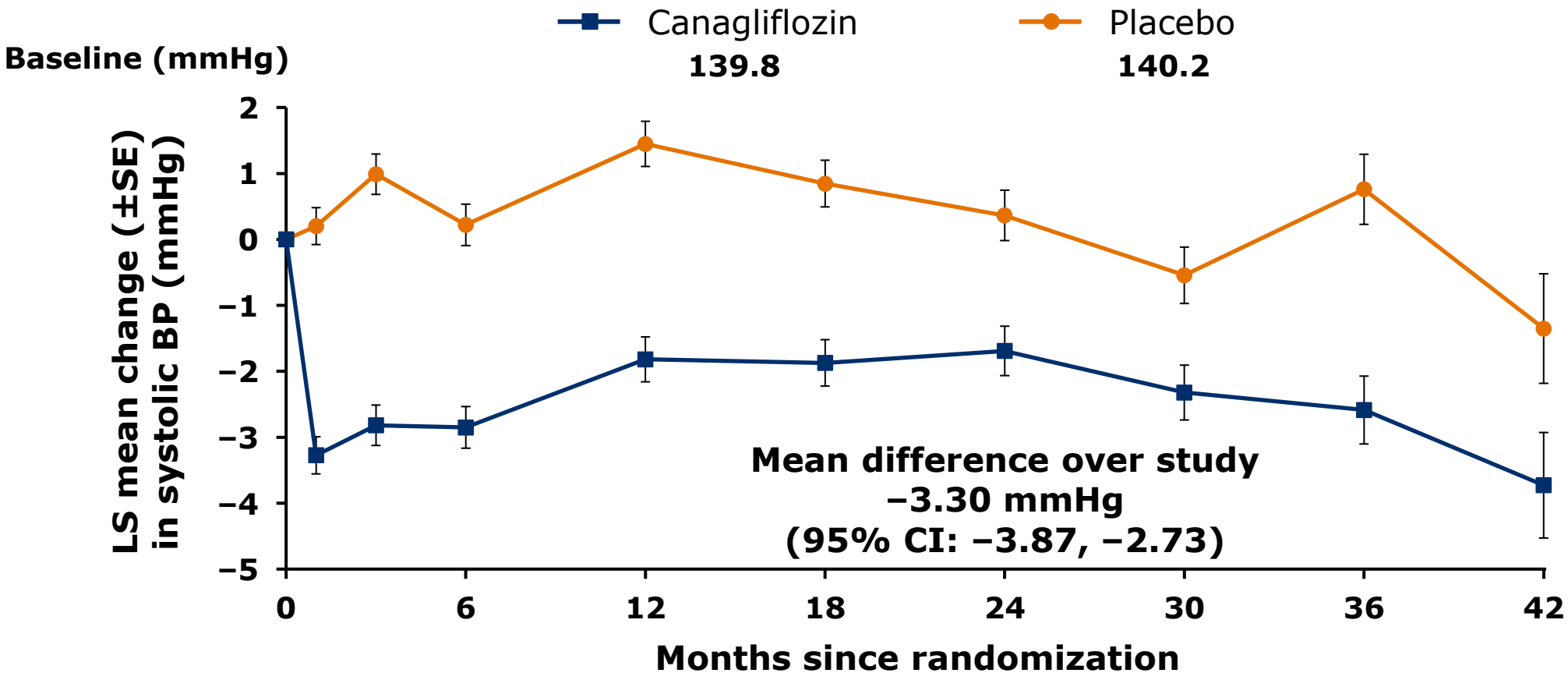


No. of participants

Placebo	2150	2103	2066	1981	1882	1728	1172	688	252
Canagliflozin	2154	2108	2074	2024	1909	1817	1254	729	274

ITT analysis

CREDENCE trial: Effects on Systolic BP



No. of participants

Placebo	2188	2131	2096	2027	1923	1766	1187	682	245
Canagliflozin	2190	2141	2096	2047	1962	1842	1261	731	264

ITT analysis

Ye N et al. *Circulation* 2020;143:1735-1749

CREDENCE

Practical issues for Nephrologists prescribing SGLT2 inhibitors:

1. Ketoacidosis

CREDENCE

	Canagliflozin (n=2200)	Placebo (n=2197)
Ketoacidosis	11 (0.5%)	1 (0.05%)

DAPA-CKD

	Dapagliflozin (n=2149)	Placebo (n=2149)
Ketoacidosis	0	2 (0.1%)

EMPA-KIDNEY

	Empagliflozin (n=3304)	Placebo (n=3305)
Ketoacidosis	6 (0.2%)	1 (0.03%)

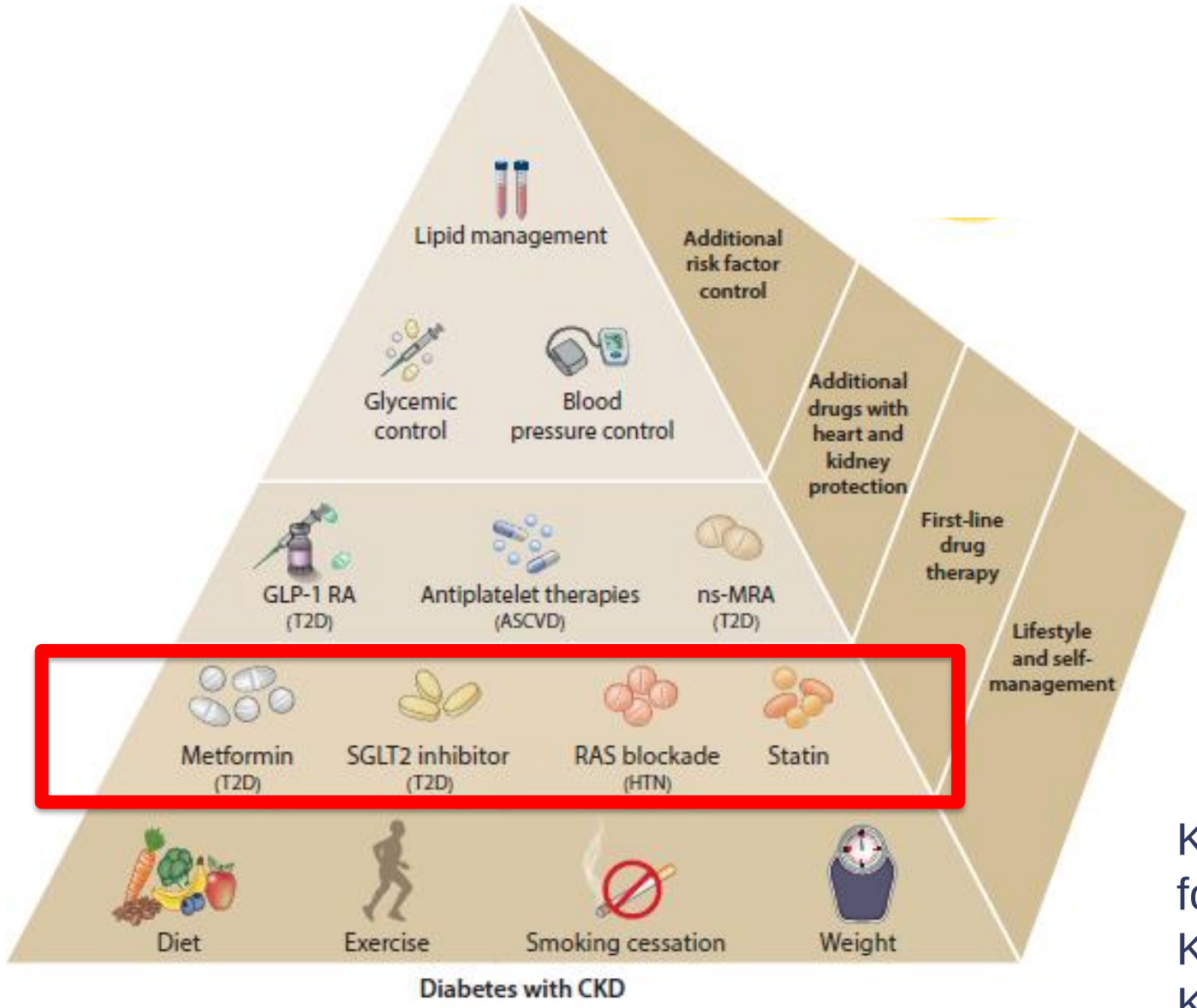
Avoid SGLT2s in type 1 diabetes

Avoid insulin dose reductions when starting SGT2 inhibitors

Beware of euglycaemic diabetic ketoacidosis (test for ketones)

Perkovic V et al. N Engl J Med 2019;380:2295-2306.
Heerspink HJL. et.al. N Engl J Med 2020;383:1436-1446
Herrington W et al. N Engl J Med 2022. DOI 10.1056 Moa2204233

KDIGO Guidelines on Management of Diabetes and CKD



First line therapy:

- Metformin
- SGLT2 Inhibitor
- RAS Blockade
- Statin

KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease.
Kidney Int. 2022;102(5S):S1–S127.

Case 2: Chinese male with progressive IgA Nephropathy

- 62 year old Chinese man with IgA Nephropathy
- Diagnosis on kidney biopsy 10 years ago
- No diabetes of cardiovascular disease
- Initial response to steroid therapy now discontinued
- Ramipril 10 mg od and Amlodipine 10 mg od for hypertension

eGFR 43 ml/min/1.73m^2 (previously 51)

UACR 98 mg/mmol (previously 75)

(UACR 867 mg/g, previously 664)

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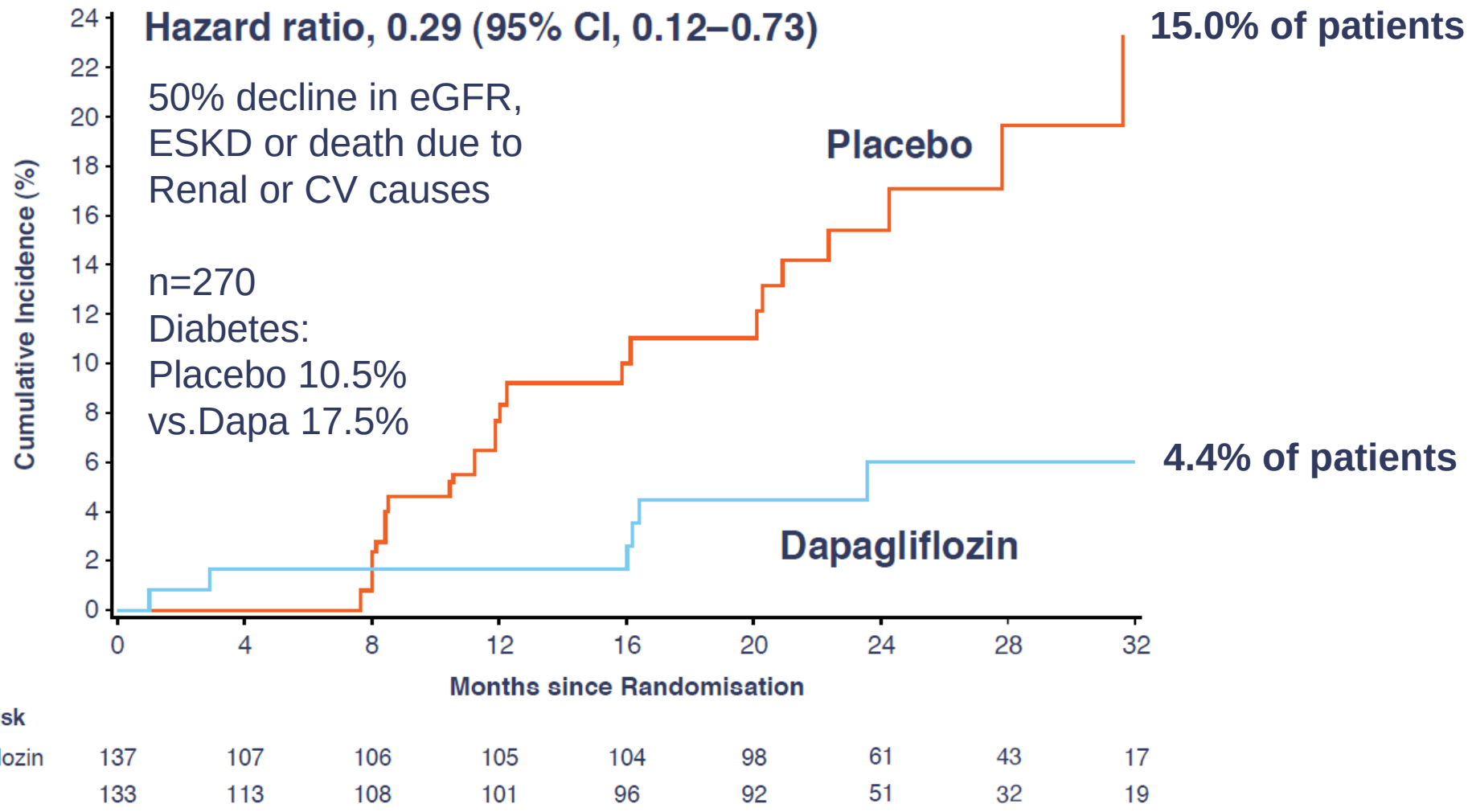
- Diagnosis on kidney biopsy 10 years ago
- No diabetes of cardiovascular disease
- Initial response to steroid therapy now discontinued
- Ramipril 10 mg od, Amlodipine 10 mg od, Dapagliflozin 10 mg od

eGFR 43 ml/min/1.73m^2 (previously 51)

UACR 98 mg/mmol (previously 75)

(UACR 867 mg/g, previously 664)

DAPA-CKD: Primary composite outcome in IgA Nephropathy



Wheeler DC et al, Kidney Int 2021 100(1):215-224.

DAPACKD

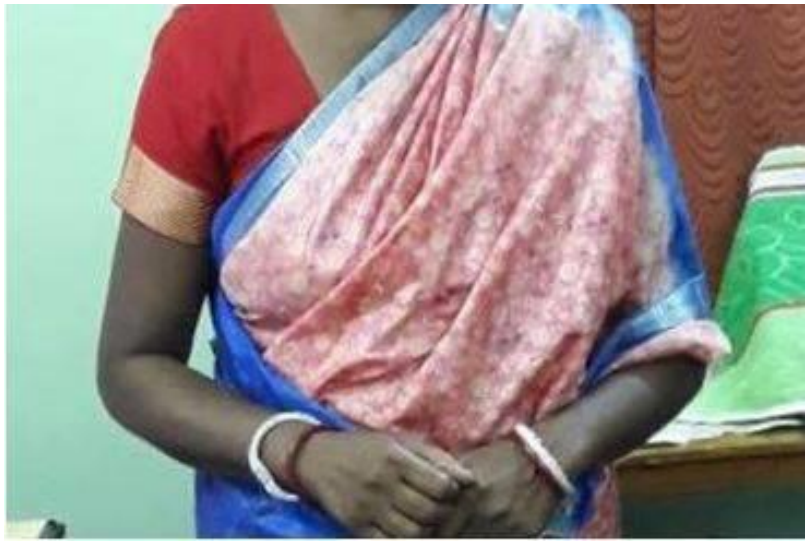
Case 3: Asian female with ischaemic Nephropathy

- 73 year Asian lady with cardiovascular disease
- Not diabetic, not overweight
- Prior inferior STEMI (primary angioplasty) with residual HFpEF
- “Small kidneys” on ultrasound scan
- Ankle oedema
- Amlodipine 10 mg od, Furosemide 40 mg od, Atorvastatin 40 mg od

eGFR 28 ml/min/1.73m^2 (previously 32)

UACR <3 mg/mmol

(UACR <27 mg/g)



Case 3: Asian female with ischaemic Nephropathy

- 73 year Asian lady with cardiovascular disease
- Not diabetic, not overweight
- Prior inferior STEMI (primary angioplasty) with residual HFpEF
- “Small kidneys” on ultrasound scan
- Peripheral vascular disease and ankle oedema
- Amlodipine 10 mg od, Furosemide 40 mg od, Atorvastatin 40 mg od
- Empagliflozin 10 mg od

eGFR 28 ml/min/1.73m^2 (previously 32)
UACR <3 mg/mmol
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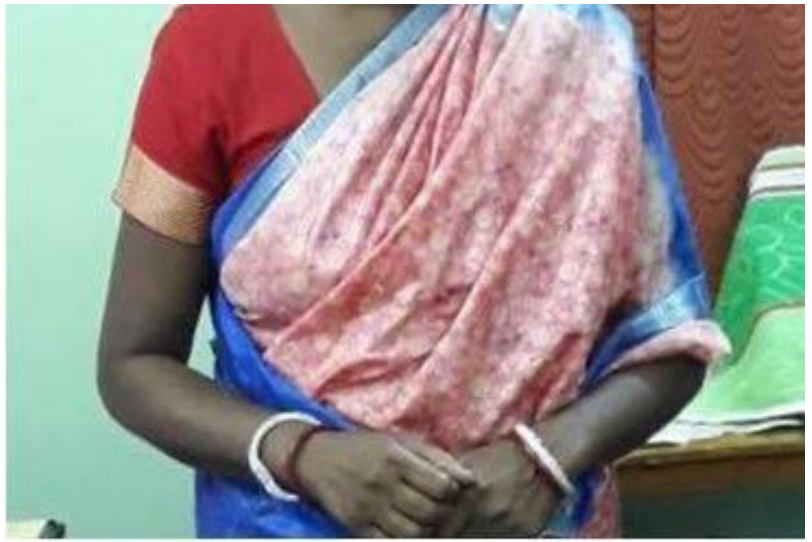
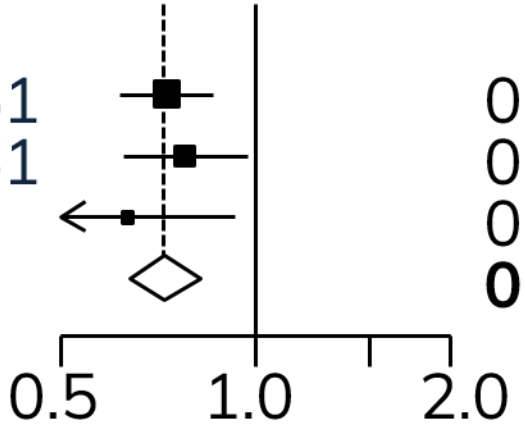


EMPA KIDNEY: Primary outcome by kidney function

eGFR mL/min/1.73m²	No. of events / participants: Empagliflozin	No. of events / participants: Placebo	Hazard Ratio (95% CI)
< 30	247/1131	317/1151	0.73 (0.62–0.86)
≥ 30 <45	140/1467	175/1461	0.78 (0.62–0.97)
≥ 45	45/706	66/693	0.64 (0.44–0.93)
All participants			**0.72 (0.64–0.82)**

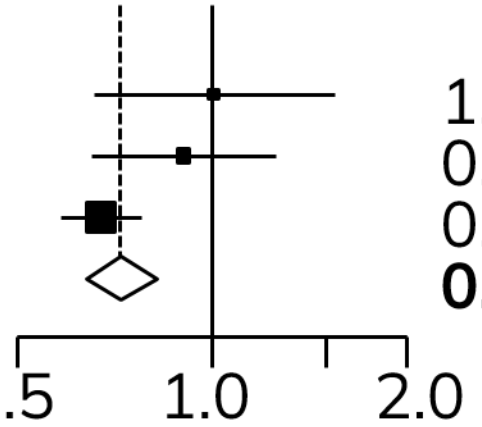


Trend P value= 0.78

EMPA-KIDNEY Collaborative Group NEJM 2022, PMID 36351458

EMPA KIDNEY: Primary outcome by albuminuria

uACR mg/g		No. of events / participants: Empagliflozin	Placebo	Hazard Ratio (95% CI)
<30	(A1)	42/665	42/663	1.01 (0.66–1.55)
≥30 ≤300	(A2)	67/927	78/937	0.91 (0.65–1.26)
>300	(A3)	323/1712	438/1705	0.67 (0.58–0.78)
All participants				**0.72 (0.64–0.82)**



Trend P value= 0.02

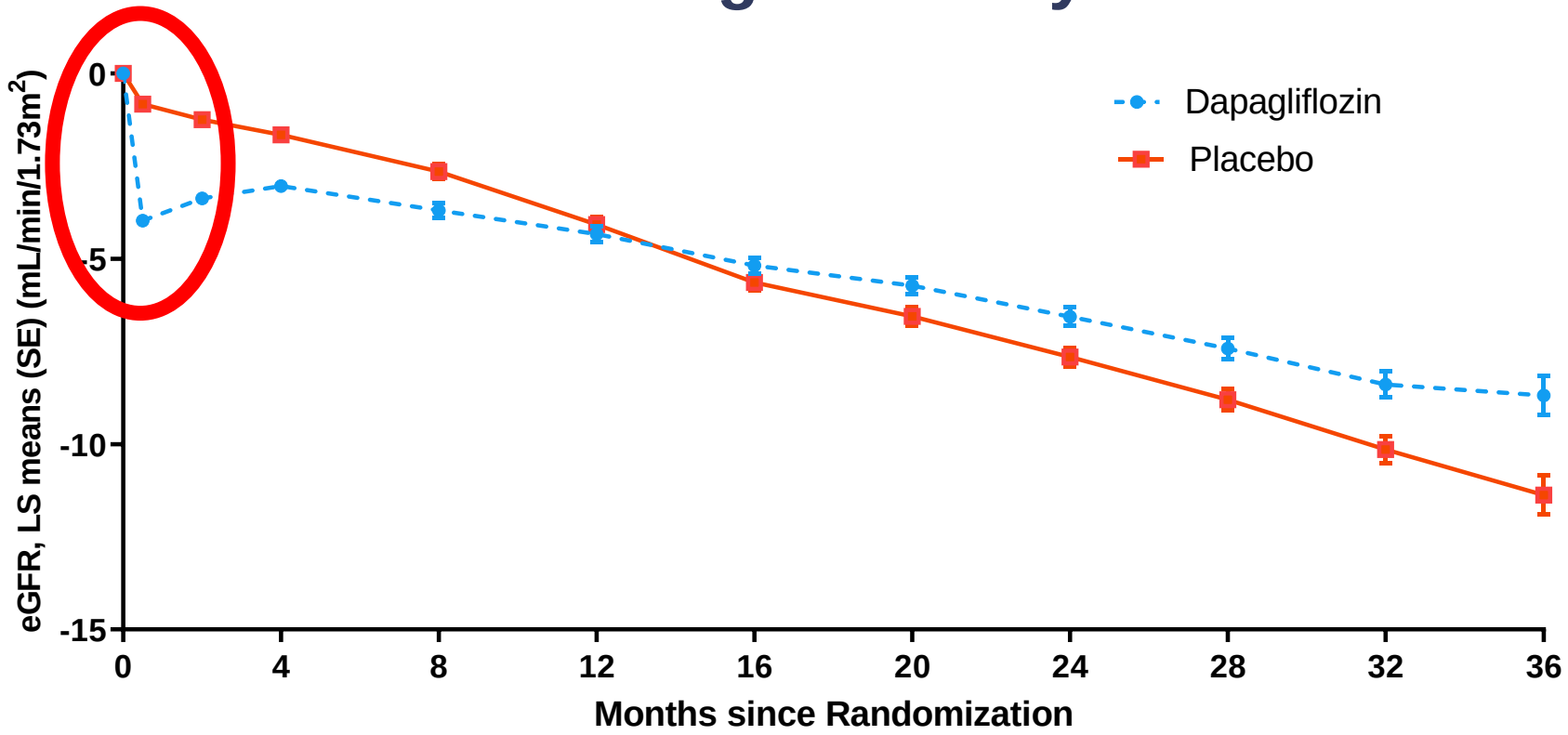
Herrington W et al, NEJM 2022, PMID 36351458

EMPA KIDNEY: Safety outcomes

Serious adverse events n (%)	Empagliflozin (N=3304)	Placebo (N=3305)	Hazard ratio (95% CI)
Urinary tract infection	52 (1.6%)	54 (1.6%)	0.94 (0.64-1.37)
Hyperkalaemia	92 (2.8%)	109 (3.3%)	0.83 (0.63-1.09)
Acute kidney injury	107 (3.2%)	135 (4.1%)	0.78 (0.60-1.00)
Ketoacidosis	6 (0.2%)	1 (<0.1%)	-
Lower limb amputation	28 (0.8%)	19 (0.6%)	1.43 (0.80-2.57)

EMPA-KIDNEY Collaborative Group ePUB Ahead of Print NEJM NOV 2022 DOI: 10.1056/NEJMoa2204233

DAPA-CKD: eGFR decline during the study



No. of Patients

Dapagliflozin	2152	2031	2001	1896	1832	1785	1705	1482	978	496	157
Placebo	2152	2029	1981	1866	1795	1753	1672	1443	935	447	157

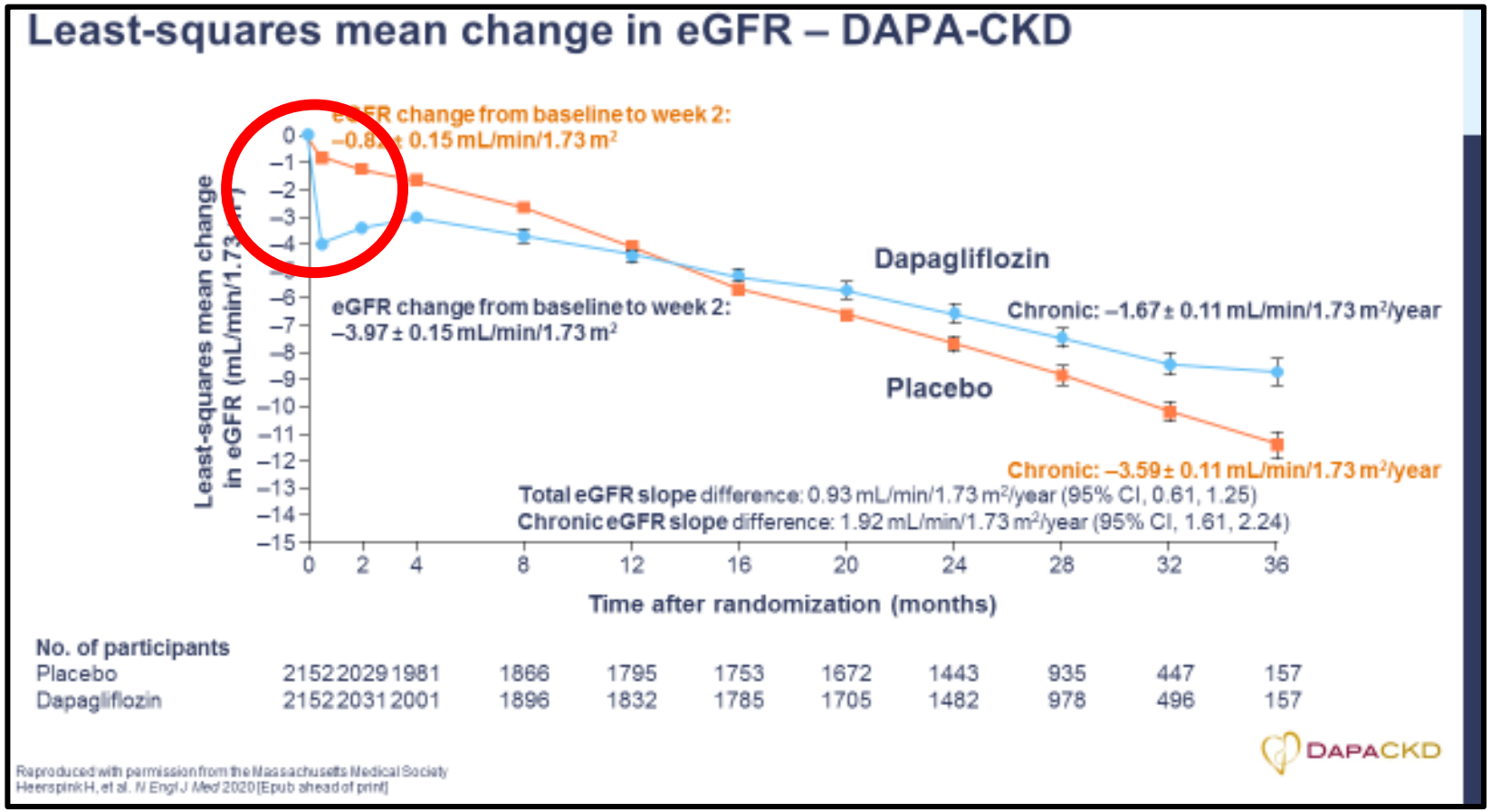
LS means eGFR slope (SE)	Dapagliflozin	Placebo	Between group difference (95% CI)
Acute, mL/min/1.73m²/2 weeks	−3.97 (0.15)	−0.82 (0.15)	
Chronic, mL/min/1.73m²/year	−2.86 (0.11)	−3.79 (0.11)	0.93 (0.61, 1.25)

CI, confidence interval; eGFR, estimated glomerular filtration rate; LS, least-squares; SE, standard error.
Heerspink HJL. et.al. *N Engl J Med* 2020;383:1436-1446.

DAPACKD

Practical issues for Nephrologists prescribing SGLT2 inhibitors:

2. Acute decline in eGFR



- Small reduction in eGFR
- Seen with ACEi/ARBs
- Haemodynamic change
- No increased risk of AKI
- Long-term eGFR benefit

If >30% reconsider
? atherosclerotic RAS

DAPACKD

Practical issues for Nephrologists prescribing SGLT2 inhibitors:
3. Volume depletion

Safety by diuretic use at baseline

Safety outcomes, n (%)	With diuretic use		Without diuretic use	
	Dapagliflozin (n=927)	Placebo (n=953)	Dapagliflozin (n=1222)	Placebo (n=1196)
Discontinuation due to adverse event	6.0	6.0	5.1	5.5
Any serious adverse event*	33.4	38.2	23.2	25.9

- Caution in patients at high risk of dehydration
- Suspend during gastrointestinal upset (diarrhoea and vomiting)

Heerspink HJL. Present at DAPA-CKD Symposium ASN 2020

DAPACKD

Take home messages: SGLT2 inhibitors in CKD

- SGLT2 inhibitors improve kidney (and cardiovascular) outcomes in a broad range of patients with chronic kidney disease both with and without type 2 diabetes.
- Benefits seem to persist at lower levels of eGFR (to 20 ml/min/1.73^2) but may be attenuated in those with lower levels of albuminuria (>3 mg/mmol or 30 mg/g).
- The safety profile appears favourable, an early reduction in eGFR is not associated with an increased risk of acute kidney injury but be cautious in patients on diuretics.
- Risks of ketoacidosis and amputation are low but real
- Avoid use in type 1 diabetes and be cautious in frail patients and those prone to dehydration. Warn patients about genital fungal infection.